

# Analytical study of an exclusive genetic switch

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**Abstract.** The nonequilibrium stationary state of an exclusive genetic switch is considered. The model comprises two competing species and a single binding site which, when bound to by a protein of one species, causes the other species to be repressed. The model may be thought of as a minimal model of the power struggle between two competing parties. Exact solutions are given for the limits of vanishing binding/unbinding rates and infinite binding/unbinding rates. A mean field theory is introduced which is exact in the limit of vanishing binding/unbinding rates. The mean field theory and numerical simulations reveal that generically bistability occurs and the system is in a symmetry broken state. An exact perturbative solution which in principle allows the nonequilibrium stationary state to be computed is also developed and computed to first and second order.

## 1. Introduction

Genetic networks are interacting, many-component systems of genes, RNA and proteins, that control the functions of living cells [1–3]. They exhibit complex, nonlinear behaviour due to the feedback between the expression of different genes. At a simplistic level of description the gene sequence, through transcription by RNA and translation by mRNA, leads to the production of proteins. These proteins may themselves act as transcription factors which may switch on or off the activity of other genes [4]. A particularly simple example of a genetic network is a toggle switch formed from pairs of genes that mutually repress each other's expressions [5]. Such switches serve as microscopic models for bistable and oscillatory states [6–9] and importantly may be synthesized [10].

Genetic switches may exhibit bistability where there are two possible dynamically stable long-lived states for the switch. There has been considerable interest in how bistability may be maintained and how it is effected by stochastic fluctuations due to small numbers of proteins and intrinsic noise [11–13]. In particular the switching time between the two states has been measured and numerical techniques have been devised to study the switching time within theoretical models [7, 14–16].

In this paper we consider the simplest toggle switch introduced by Warren and P.R. ten Wolde [6] which we will refer to as the Exclusive Switch (this model is referred to in [7] as the exclusive switch without cooperative binding). The model comprises two genes labelled 1,2 each leading to the production of proteins  $X_1$  and  $X_2$ . These proteins also degrade stochastically. There is a single mutual binding site to which either an  $X_1$  or  $X_2$  may bind and when bound repress the production of the other protein. Thus when an  $X_1$  is bound, the  $X_1$  population fluctuates around some steady state value determined by the balance of production and degradation while the  $X_2$  population degrades towards zero.

This switch may be considered more generally as a minimal model for the power struggle between two competing parties. This is illustrated by the following caricature of “mob dynamics”. There are two competing parties or gangs of individuals and room for only one individual to wield absolute power. When an individual of one party is in power his own party membership may grow but the other party membership dwindles. Random influences imply that the control of power is occasionally lost and power may be seized by any individual. Thus in a temporary power vacuum the membership of the minority party will increase and there is a small chance that a member of this party will seize power and that the minority will eventually become the majority.

In the context of statistical physics the Exclusive Switch is an example of a nonequilibrium system. This is because the microscopic stochastic dynamics do not obey detailed balance. For example when an  $X_1$  protein is bound the degradation of an  $X_2$  protein is irreversible. The structure of nonequilibrium stationary states has been of considerable interest and is generally characterised by the existence of probability currents in the stationary state (which do not exist in equilibrium stationary states

due to the presence of detailed balance) [17]. For example it has been shown that spontaneous symmetry breaking may occur in non-equilibrium systems under conditions where it is precluded from their equilibrium counterparts e.g. in one spatial dimension [18, 19].

The bistability exhibited in the Exclusive Switch may be thought of as symmetry breaking where although the microscopic dynamics is symmetric between the two proteins, the stationary state comprises two possible long-lived dynamical states in which the symmetry is broken and one protein dominates. In an equilibrium system the switching time between the two symmetry-broken states may be estimated by the Arrhenius law  $\tau \sim \exp \beta \Delta F$  where the free energy barrier  $\Delta F$  is extensive in the system size. For a nonequilibrium system on the other hand the free energy or indeed the stationary state is not known a priori and one is required to construct the stationary state on a model by model basis. For genetic switches there has been recent interest in developing analytical approaches to describe the stationary states [20, 21].

In the present work we study analytically the nonequilibrium stationary state of the Exclusive Switch. Previous analytical studies have concentrated on systems with only one gene [20, 22, 23]. Our aim is to understand whether symmetry breaking occurs and, if so, the nature of the symmetry broken state. To this end we develop two analytical approaches. First we construct a mean field theory. Then we develop a perturbative approach that in principle allows the nonequilibrium stationary state to be computed exactly and we present analytical results to first order. A complementary approach to this system has been developed in [24], where an approximation scheme based on effective interactions is used.

The paper is organised as follows. In section 2 we define the Exclusive Switch model and write down the system of master equations that describe the system. We also present some numerical simulations which illustrate the nature of the symmetry breaking and consider exactly solvable limits. In section 3 we present a mean field theory and compare to stochastic simulations. In section 4 we develop a perturbative approach, compute the results to first order and compare with simulation results. Conclusions are drawn in section 5.

## 2. Model Definition

The state of the system is defined by: the number of free proteins of type 1,  $N_1$ ; the number of free proteins of type 2,  $N_2$ , and the state of the switch,  $S$ , which takes value 0 if no protein is bound, value 1 if a protein of type 1 is bound, and value 2 if a protein of type 2 is bound.

The stochastic dynamical processes are as follows: a protein degrades (leaves the system) with rate  $d$ ; when the switch state is 0 proteins of both type 1 and 2 are produced with rate  $g$ ; when the switch state is 1 proteins of type 1 produced with rate  $g$  and when the switch state is 2 proteins of type 2 produced with rate  $g$ ; if the switch state is 0 a protein binds with rate  $b$  and when binding occurs the switch state changes

to the type of bound protein and the number of free proteins is reduced by 1; a bound protein unbinds with rate  $u$  and when unbinding occurs the switch state changes to 0 and the number of free proteins is increased by 1.

We shall consider the joint probabilities  $P_S(N_1, N_2)$  of the protein numbers  $N_1, N_2$ , switch state  $S$ .

### 2.1. Master equation

Following the stochastic dynamical processes described above the system of master equations that defines the model can be written as follows

$$\begin{aligned} \frac{\partial P_0}{\partial t}(N_1, N_2) = & g[P_0(N_1 - 1, N_2) + P_0(N_1, N_2 - 1) - 2P_0(N_1, N_2)] \\ & + d[(N_1 + 1)P_0(N_1 + 1, N_2) + (N_2 + 1)P_0(N_1, N_2 + 1) \\ & - (N_1 + N_2)P_0(N_1, N_2)] - b(N_1 + N_2)P_0(N_1, N_2) \\ & + u[P_1(N_1 - 1, N_2) + P_2(N_1, N_2 - 1)] \end{aligned} \quad (1)$$

$$\begin{aligned} \frac{\partial P_1}{\partial t}(N_1, N_2) = & g[P_1(N_1 - 1, N_2) - P_1(N_1, N_2)] \\ & + d[(N_1 + 1)P_1(N_1 + 1, N_2) + (N_2 + 1)P_1(N_1, N_2 + 1) \\ & - (N_1 + N_2)P_1(N_1, N_2)] \\ & + b(N_1 + 1)P_0(N_1 + 1, N_2) - uP_1(N_1, N_2) \end{aligned} \quad (2)$$

$$\begin{aligned} \frac{\partial P_2}{\partial t}(N_1, N_2) = & g[P_2(N_1, N_2 - 1) - P_2(N_1, N_2)] \\ & + d[(N_1 + 1)P_2(N_1 + 1, N_2) + (N_2 + 1)P_2(N_1, N_2 + 1) \\ & - (N_1 + N_2)P_2(N_1, N_2)] \\ & + b(N_2 + 1)P_0(N_1, N_2 + 1) - uP_2(N_1, N_2) \end{aligned} \quad (3)$$

where  $g$  is the generation rate of a protein (when the generation is not suppressed by the switch state),  $d$  is the degeneration rate of a single protein,  $b$  is the binding rate of a single protein and  $u$  is the unbinding rate of the bound protein. The whole problem is clearly symmetric with respect to the variables 1 and 2. Also note that, the degeneration term is the same for the three equations, since it does not depend on the value of  $S$ .

### 2.2. Nature of symmetry breaking

In order to illustrate the qualitative behaviour, we first present stochastic simulations of the Exclusive Switch. These simulations are performed with a Gillespie algorithm [25, 26], in which the reactions described in the model are given a certain probability, depending on the state of the system and the value of the parameters. These probabilities are used to determine stochastically which reaction is going to happen next, and when it will happen. The time that the system spends in a given state  $N_1, N_2, S$  is normalized to obtain the probability distributions. The reference values for the simulations are the typical values for bacteria such as *Escherichia coli* [1]

$$g = 0.05, \quad d = 0.005, \quad b = 0.1, \quad u = 0.005 \quad (4)$$

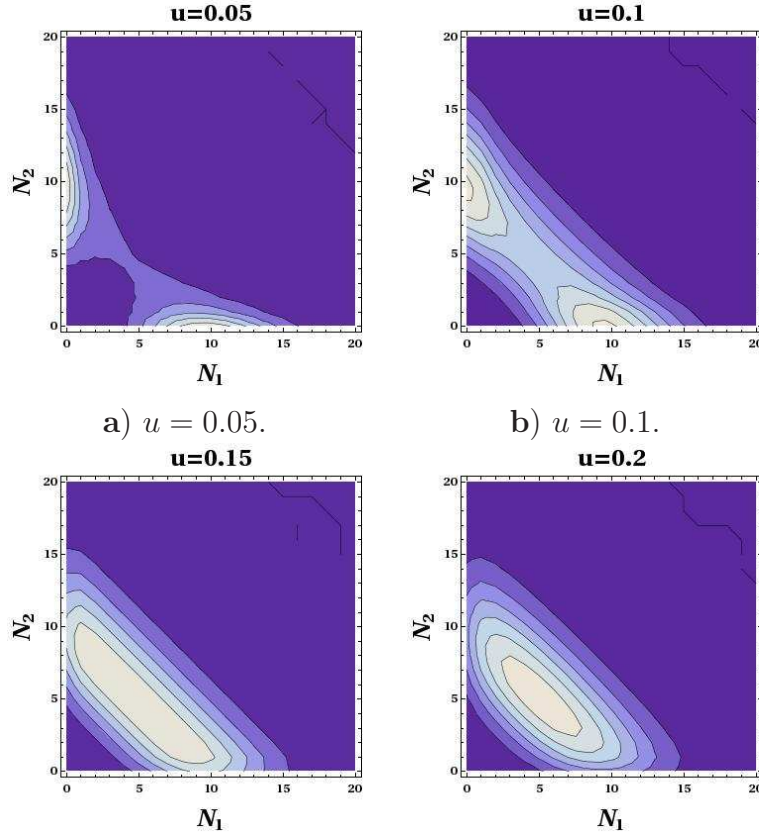
In the system there is a clear symmetry between the two proteins species, since they undergo the same microscopic reactions. However, at any given time the system is typically dominated by one of the proteins; thus the symmetry is broken. The reason for this is that, once a protein, e.g. of type  $X_1$ , binds to the promoter site, proteins  $X_2$  start disappearing, while the number of  $X_1$  fluctuates around a steady value. That means that when the bound protein unbinds (as it will do eventually due to stochasticity of the system), it is much more probable for proteins  $X_1$  to bind to the promoter site again, since there are more of them. At the same time it is more difficult for proteins  $X_2$  to bind to the promoter site. However the  $X_2$  will not disappear permanently from the system (there is no absorbing state), and will be produced again the moment the bound protein  $X_1$  unbinds. Thus, with a small probability, proteins  $X_2$  will be able to bind again to the promoter site, and become the dominant species, as proteins  $X_1$  start to degenerate. This means that there are two symmetry-broken states, in which one species is much more abundant than the other.

With regard to the probability distribution  $P(N_1, N_2)$ , this bistability is translated into two peaks, concentrated around the axes, i.e. where one of the protein numbers is almost zero. This is illustrated in a contour plot in figure 1 for  $u = 0.05$ . However, this bistability depends strongly on the value of the parameters: the bigger the value of  $u$ , the more irrelevant is the switch state for the dynamics of the protein, and the less important is the bistability we have described. For example in figure 1, when  $g, b$  and  $d$  are kept constant and  $u$  is increased, the peaks move together and eventually merge at some value of  $u \simeq 0.15$ . Thus there is an apparent transition from a distribution with two symmetry-related peaks to a distribution with one symmetric peak. We wish to study the nature of this transition i.e. is there an underlying phase transition at a finite value of  $u$  where the system changes from symmetry-broken behaviour to symmetric behaviour, or is the transition simply due to two peaks coming closer together and no longer being resolved? The latter would correspond to a ‘geometrical transition’ in the form of  $P(N_1, N_2)$  but would not correspond to any underlying phase transition.

Although the whole probability distribution is always symmetric, distributions  $P_1$  and  $P_2$  will be a priori asymmetric, since they describe the probability of the number of proteins when a protein 1 or 2 are bound, which are not symmetric situations. Let us now define  $r_A$  and  $r_B$  as the probability masses of  $P_1$  on either sides of the diagonal  $N_1 = N_2$  :

$$\begin{aligned} r_A &= \sum_{N_1 > N_2} P_1(N_1, N_2) + \frac{1}{2} \sum_{N_1 = N_2} P_1(N_1, N_2) \\ r_B &= \sum_{N_1 < N_2} P_1(N_1, N_2) + \frac{1}{2} \sum_{N_1 = N_2} P_1(N_1, N_2) . \end{aligned} \tag{5}$$

We can now study how  $r_A$ ,  $r_B$  change with  $u$ , and whether there is a clear transition between the situation in which they are different, and the one in which they are equal to each other (if there is any). Figure 2 shows that these two quantities approach each other in a continuous way, and they are equal only when  $u \rightarrow \infty$ , that is, when the



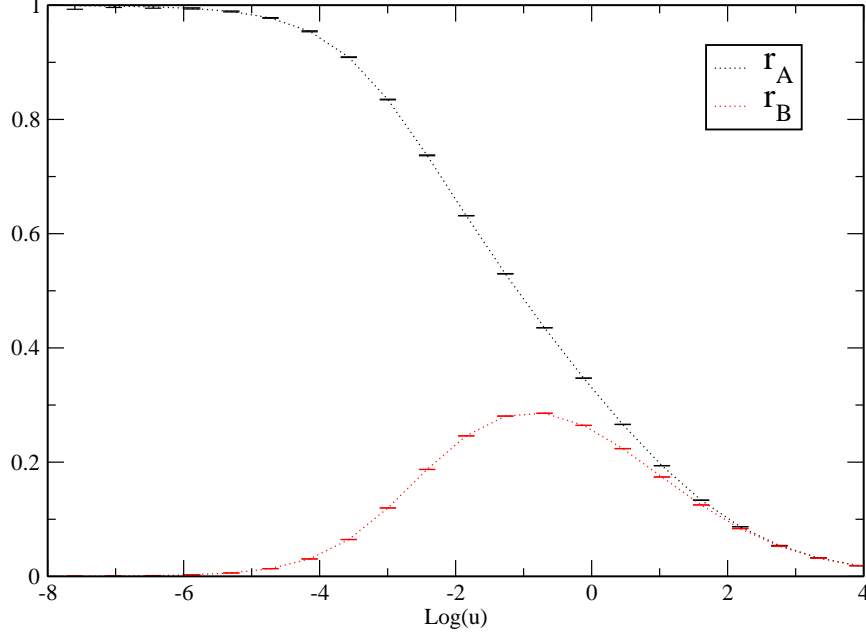
**Figure 1.** Contour plot of probability distribution  $P(N_1, N_2)$  obtained from stochastic simulations. A Transition from a two peak regime to a one peak regime occurs as the unbinding parameter  $u$  increases.  $g, b$  and  $d$  are kept equal to the E. coli values (4)

only possible state of the switch is  $S = 0$  and it has no longer any effect on the protein dynamics. Therefore, the probability distributions  $P_1, P_2$  and hence  $r_A, r_B$  tend to zero, all the probability being concentrated in the distribution  $P_0(N_1, N_2)$ , which is always symmetric.

Despite the fact that a change in the shape of the distribution is observed (figure 3), there is no evidence of the typical singularities that appear in a phase transition. Instead  $P_1$  appears to deform continuously into a symmetric distribution when  $u \rightarrow \infty$ . We conclude that (at least for these parameter values)  $P_1(N_1, N_2)$  remains asymmetric for  $u < \infty$ , and as a consequence so does  $P_2$ , and there is no transition to a symmetric state in this marginal distribution. As figure 3 shows,  $P_1$  has only one peak for different values of  $u$ , and even if it becomes smaller as  $u$  increases, it does not become symmetric at any point.

We deduce that, even though  $P(N_1, N_2)$  appears to become symmetric at some finite value of  $u$  (see figure 1), there is no true phase transition between symmetric and asymmetric regimes, since  $P_1$  and  $P_2$  always remain asymmetric. Thus, the bistability of the switch is always present, with the asymmetric distributions  $P_1, P_2$  decreasing as the switch state becomes less important, that is, as  $u$  increases.

**Figure 2.** Evolution of the two contributions to  $P_1(N_1, N_2)$  defined in (5)— $r_A$  for  $N_1 > N_2$  and  $r_B$  for  $N_1 < N_2$ —as  $u$  increases.



### 2.3. Solution in limit $u, b \rightarrow 0$

We now consider the system in the limit  $u, b \rightarrow 0$  with the binding constant

$$k = \frac{b}{u} \quad (6)$$

held fixed. In this limit the system will equilibrate between binding/unbinding events. When the switch is in state 1 the number of type 2 proteins decays to zero and the number of type 1 is given by Poissonian statistics for the generation/degeneration processes:

$$P_1(N_1, N_2) = r_1 \frac{1}{N_1!} \left(\frac{g}{d}\right)^{N_1} e^{-g/d} \delta_{N_2,0} \quad (7)$$

where  $r_1$  is the probability of the switch being in state 1 ( $r_1 = \sum_{N_1, N_2=0}^{\infty} P_1(N_1, N_2)$ ). Similarly, in state 2 the number of type 2 is given by Poissonian statistics

$$P_2(N_1, N_2) = r_2 \frac{1}{N_2!} \left(\frac{g}{d}\right)^{N_2} e^{-g/d} \delta_{N_1,0} \quad (8)$$

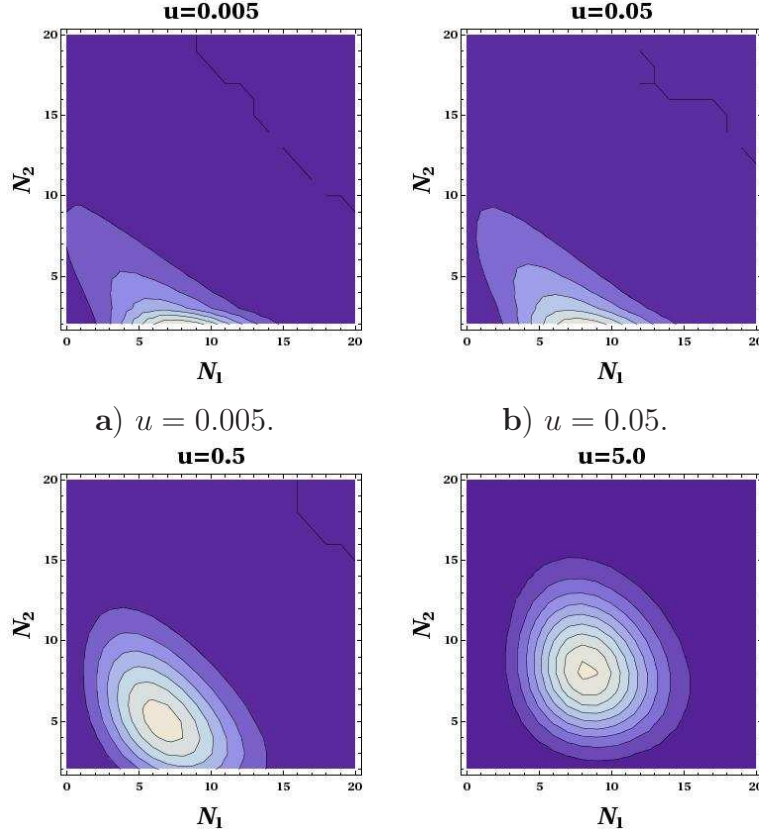
and in state 0 both  $N_1$  and  $N_2$  are given by Poissonian statistics

$$P_0(N_1, N_2) = r_0 \frac{1}{N_1! N_2!} \left(\frac{g}{d}\right)^{N_1+N_2} e^{-2g/d}. \quad (9)$$

In order to fix the probabilities  $r_0, r_1, r_2$  we consider the master equation for  $r_1$  which can be obtained from summing (2) over the variables  $N_1, N_2$ :

$$\dot{r}_1 = -ur_1 + b\overline{N_1^0} \quad (10)$$





**Figure 3.** Contour plots for the probability distribution  $P_1(N_1, N_2)$ , for different values of  $u$ . As  $u$  increases, the peak of the distribution moves towards the diagonal  $N_1 = N_2$ , but the distribution is not completely symmetric as long as  $u$  is finite. Also, the probability mass of the distribution decays as  $u$  increases, and is transferred to the symmetrical distribution  $P_0(N_1, N_2)$ .

where the quantity  $\overline{N_1^0}$  is the mean value of  $N_1$  given the system is in switch state  $S = 0$ , multiplied by the probability of being in switch state  $S = 0$ , i.e,  $\overline{N_1^0} = \sum_{N_1, N_2=0}^{\infty} N_1 P_1(N_1, N_2)$ . In the stationary state we have  $\overline{N_1^0} = r_0 g/d$  and (10) becomes

$$0 = -ur_1 + \frac{bg}{d}r_0. \quad (11)$$

A similar equation holds for  $r_2$  and the normalisation of probability yields

$$r_0 = \frac{1}{1 + 2kg/d} \quad r_1 = r_2 = \frac{kg/d}{1 + 2kg/d}. \quad (12)$$

Thus we see that the system has three long-lived states: when  $S = 1$  the system is dominated by type 1 proteins; when  $S = 2$  the system is dominated by type 2 proteins, and when  $S = 0$  the system is in a symmetric state.

When  $k \rightarrow \infty$  the symmetric state has zero weight ( $r_0 \rightarrow 0$ ) and the system is either in the  $S = 1$  state or the  $S = 2$  state. The switching time between the two states is expected to diverge in this limit therefore the system exhibits symmetry breaking. Note that the transition from the  $S = 1$  state to the  $S = 2$  state is through the symmetric  $S = 0$  state.



2.4. Solution in limit  $u, b \rightarrow \infty$ 

In this limit the unbinding and binding events happen on a faster time scale than the growth and degradation of proteins. Therefore the switch state becomes decoupled from the numbers of protein and the probabilities obey

$$P_S(N_1, N_2) = P(N_1, N_2)r_S(N_1, N_2) \quad (13)$$

where  $P(N_1, N_2)$  is the probability of  $N_1, N_2$  proteins being in the system regardless of switch state. That is, for given number of proteins  $N_1$  and  $N_2$  (which include any bound protein) the switch probabilities equilibrate and obey

$$ur_1(N_1, N_2) = bN_1r_0(N_1, N_2) \quad ur_2(N_1, N_2) = bN_2r_0(N_1, N_2) \quad (14)$$

which may be solved to obtain

$$r_0 = [1 + k(N_1 + N_2)]^{-1} \quad r_1 = kN_1r_0 \quad r_2 = kN_2r_0 \quad (15)$$

where the binding constant  $k$  is given by (6).

A master equation for the evolution of  $P(N_1, N_2)$  on the slower timescale on which generation and degeneration events occur may then be written down:

$$\begin{aligned} \frac{\partial P}{\partial t}(N_1, N_2) = & g[1 - r_2(N_1 - 1, N_2)]P(N_1 - 1, N_2) - d[N_1 - r_1(N_1, N_2)]P(N_1, N_2) \\ & - g[1 - r_2(N_1, N_2)]P(N_1, N_2) + d[N_1 + 1 - r_1(N_1 + 1, N_2)]P(N_1 + 1, N_2) \\ & + g[1 - r_1(N_1, N_2 - 1)]P(N_1, N_2 - 1) - d[N_2 - r_2(N_1, N_2)]P(N_1, N_2) \\ & - g[1 - r_1(N_1, N_2)]P(N_1, N_2) + d[N_2 + 1 - r_2(N_1, N_2 + 1)]P(N_1, N_2 + 1). \end{aligned} \quad (16)$$

The terms with coefficient  $g$  in (16) represent generation of  $N_i$  when the switch is not in switch state  $i$ . The terms with coefficient  $d$  in (16) represent reduction of  $N_i$  with rate  $dN_i$  when the switch is not state  $i$  and reduction with rate  $d(N_i - 1)$  when the switch is in state  $i$  (this is because the bound protein does not degrade). The stationary state of (16) obeys detailed balance with respect to generation and degradation of  $N_1$  and  $N_2$  individually, thus

$$\begin{aligned} P(N_1, N_2) &= P(N_1 - 1, N_2) \frac{g[1 - r_2(N_1 - 1, N_2)]}{d[N_1 - r_1(N_1, N_2)]} \\ &= P(N_1 - 1, N_2) \frac{g}{d} \frac{[1 + k(N_1 - 1)]}{[1 + k(N_1 + N_2 - 1)]} \frac{1}{N_1} \frac{[1 + k(N_1 + N_2)]}{[1 + k(N_1 + N_2 - 1)]} \end{aligned} \quad (17)$$

with a similar equation holding for detailed balance in  $N_2$ . Then these equations may be iterated to obtain

$$\begin{aligned} P(N_1, N_2) &= \left(\frac{g}{d}\right)^{N_1} \frac{(1 + k(N_1 + N_2))}{(1 + kN_2)} \frac{1}{N_1!} \prod_{n_1=0}^{N_1-1} \frac{(1 + kn_1)}{1 + k(N_2 + n_1)} P(0, N_2) \\ &= \left(\frac{g}{d}\right)^{N_1+N_2} \frac{(1 + k(N_1 + N_2))}{N_1!N_2!} \frac{\prod_{n_1=0}^{N_1-1} (1 + kn_1) \prod_{n_2=0}^{N_2-1} (1 + kn_2)}{\prod_{n=0}^{N_1+N_2-1} (1 + kn)} P(0, 0). \end{aligned} \quad (18)$$

The constant  $P(0, 0)$  will be determined by normalisation of the sum of probabilities to one.

The expression (18) is a single-peaked distribution which is symmetric in  $N_1$  and  $N_2$ . To see this one can identify the stationary points of  $P(N_1, N_2)$  through the conditions  $P(N_1 + 1, N_2) = P(N_1, N_2)$  and  $P(N_1, N_2 + 1) = P(N_1, N_2)$  which yield

$$\begin{aligned} \frac{g}{d} \frac{1}{(N_1 + 1)} \frac{(1 + kN_1)}{(1 + k(N_1 + N_2))} \frac{(1 + k(N_1 + N_2 + 1))}{(1 + k(N_1 + N_2))} &= 1 \\ \frac{g}{d} \frac{1}{(N_2 + 1)} \frac{(1 + kN_2)}{(1 + k(N_1 + N_2))} \frac{(1 + k(N_1 + N_2 + 1))}{(1 + k(N_1 + N_2))} &= 1. \end{aligned} \quad (19)$$

The solution of these equations is  $N_1 = N_2 = N/2$  where, when  $N$  is large,

$$kN^2 + \left[1 - k\frac{g}{d}\right] N - 2\frac{g}{d} = 0. \quad (20)$$

Thus, in the  $u, b \rightarrow \infty$  limit the system has reached a symmetric state with the probability distribution peaked at  $N_1 = N_2 = N/2$ .

### 3. Mean Field Theory

In this section we develop a mean field theory in which some correlations in the numbers of proteins are ignored.

#### 3.1. Exact Moment Equations

We start from the exact master equations (1–3) for the evolution of probabilities  $P_S(N_1, N_2)$ . The zeroth moments of  $N_i$  are the probabilities  $r_S$  i.e.

$$r_S = \sum_{N_1=0, N_2=0}^{\infty} P_S(N_1, N_2) \quad \text{for } S = 0, 1, 2. \quad (21)$$

We now define the first moments of  $\overline{N_i^S}$  of  $N_i$  as follows

$$\overline{N_i^S} = \sum_{N_1=0, N_2=0}^{\infty} N_i P_S(N_1, N_2) \quad \text{for } i = 1, 2 \quad S = 0, 1, 2 \quad (22)$$

and the second moments

$$\overline{(N_i N_j)^S} = \sum_{N_1=0, N_2=0}^{\infty} N_i N_j P_S(N_1, N_2) \quad \text{for } i, j = 1, 2 \quad S = 0, 1, 2. \quad (23)$$

Summing (1) gives

$$\frac{\partial r_0}{\partial t} = -b(\overline{N_1^0} + \overline{N_2^0}) + u[r_1 + r_2] \quad (24)$$

$$\frac{\partial \overline{N_1^0}}{\partial t} = gr_0 - d\overline{N_1^0} - b[(\overline{N_1 N_1})^0 + (\overline{N_1 N_2})^0] + u[(\overline{N_1})^1 + (\overline{N_1})^2 + r_1]. \quad (25)$$

Note that the physical meaning of e.g.  $\overline{N_i^S}$  is the probability of being in switch state  $S$  ( $r_S$ ) multiplied by the mean number of type  $i$ , *given* that the switch is in state  $S$ .

Similarly, summing (2) gives

$$\frac{\partial r_1}{\partial t} = +b\overline{N_1^0} - ur_1 \quad (26)$$

$$\frac{\partial \overline{N_1^1}}{\partial t} = gr_1 - d\overline{N_1^1} + b\overline{(N_1(N_1 - 1))^0} - u\overline{(N_1)^1} \quad (27)$$

$$\frac{\partial \overline{N_2^1}}{\partial t} = -d\overline{N_2^1} + b\overline{(N_1 N_2)^0} - u\overline{(N_2)^1}. \quad (28)$$

We now invoke symmetry between switch state 1 and 2 :

$$r_1 = r_2 = (1 - r_0)/2 \quad \overline{N_1^0} = \overline{N_2^0} \quad \overline{N_1^1} = \overline{N_2^1} \quad \overline{N_1^2} = \overline{N_2^2}. \quad (29)$$

Then the exact steady-state versions of equations (24–28) read

$$r_1 = \frac{b\overline{N_1^0}}{u} \quad r_0 = 1 - 2r_1 \quad (30)$$

$$b[\overline{(N_1 N_1)^0} + \overline{(N_1 N_2)^0}] = gr_0 - d\overline{N_1^0} + u[\overline{(N_1)^1} + \overline{(N_1)^2} + r_1] \quad (31)$$

$$b\overline{(N_1 N_1)^0} = -gr_1 + (d + u)\overline{N_1^1} + b\overline{(N_1)^0} \quad (32)$$

$$b\overline{(N_1 N_2)^0} = (d + u)\overline{N_2^1}. \quad (33)$$

Note that if we sum (31–33) we obtain the exact relation

$$d(\overline{N_1^0} + \overline{N_1^1} + \overline{N_1^2}) = g(1 - r_1) = g(1 - r_2) \quad (34)$$

which simply gives the overall birth/death balance for  $N_1$ . Also note that (32,33) give exact relations between the second moments and first moments. However to actually evaluate these moments one would have to consider equations for higher moments, leading to a hierarchy of equations.

### 3.2. Mean Field Approximation

We now make a mean-field approximation that expresses second moments in terms of first moments:

$$\overline{(N_1 N_1)^0} = \frac{\overline{N_1^0} \overline{N_1^0}}{r_0} + \overline{N_1^0} \quad (35)$$

$$\overline{(N_1 N_2)^0} = \frac{\overline{N_1^0} \overline{N_2^0}}{r_0} = \frac{(\overline{N_1^0})^2}{r_0}. \quad (36)$$

Note that a symmetry condition from (29) has been explicitly used in the last equation of (36). The first relation (35) comes from the assumption that  $N_1$  has a Poisson distribution when the switch is in the 0 state. This means that the second moment is equal to the square of the mean plus the mean itself. However, there is an important factor  $r_0$ , which comes from the fact that  $\overline{(N_1 N_1)^0}/r_0$  is the mean square value of  $N_1$  *given* that the switch is in the 0 state and  $\overline{N_1^0}/r_0$  is the mean value of  $N_1$  *given* that the switch is in the 0 state. The Poisson approximation is in fact exact in the limit where  $u, b$  tend to zero (see section 2.3).

The second relation (36) is a simple factorization scheme which ignores correlations between the values of  $N_1$  and  $N_2$  when the switch state is 0.

Using this approximation scheme (32) becomes

$$\overline{N}_1^1 = \frac{b}{d+u} \frac{(\overline{N}_1^0)^2}{r_0} + \frac{gr_1}{d+u} = \frac{br_0}{d+u} \left[ \left( \frac{\overline{N}_1^0}{r_0} \right)^2 + \frac{g}{u} \left( \frac{\overline{N}_1^0}{r_0} \right) \right] \quad (37)$$

and (33) becomes

$$\overline{N}_1^2 = \frac{br_0}{d+u} \left( \frac{\overline{N}_1^0}{r_0} \right)^2. \quad (38)$$

Using expressions (37) and (38) in (31), combined with the previous approximations (35) and (36) yields the following quadratic equation for  $\overline{N}_1^0/r_0$ :

$$\frac{2bd}{d+u} \left( \frac{\overline{N}_1^0}{r_0} \right)^2 + \left[ d - \frac{bg}{d+u} \right] \left( \frac{\overline{N}_1^0}{r_0} \right) - g = 0. \quad (39)$$

One must take the positive root of this quadratic which yields

$$\frac{\overline{N}_1^0}{r_0} = \frac{1}{4bd} \left[ bg - d(d+u) + ((d(d+u) - bg)^2 + 8bdg(d+u))^{1/2} \right]. \quad (40)$$

Then using (30) one obtains

$$r_0 = \left[ 1 + \frac{2b}{u} \frac{\overline{N}_1^0}{r_0} \right]^{-1} \quad (41)$$

$$\overline{N}_1^0 = \left( \frac{\overline{N}_1^0}{r_0} \right) \left[ 1 + \frac{2b}{u} \frac{\overline{N}_1^0}{r_0} \right]^{-1}. \quad (42)$$

One may check the limits of section 2 from the quadratic (39). In the limit  $b, u \rightarrow 0$  with  $k = b/u$  one obtains  $\overline{N}_1^0/r_0 = g/d$  and  $r_0 = [1 + \frac{2kg}{d}]^{-1}$  in agreement with Section 2.3 where it is shown that  $N_1$  follows a Poisson distribution with mean  $g/d$  when the switch is in state  $S = 1$  or  $S = 0$ .

In the limit  $b, u \rightarrow \infty$  with  $k = b/u$  fixed the quadratic (39) reduces to

$$\left( \frac{\overline{N}_1^0}{r_0} \right)^2 2kd + \frac{\overline{N}_1^0}{r_0} (d - kg) - g = 0. \quad (43)$$

This quadratic for  $\frac{\overline{N}_1^0}{r_0}$  is the same as the quadratic (20) for the value of  $N = 2N_1$  that maximises  $P(N_1, N_2)$  in the exact solution of section 2.4.

### 3.3. Comparison to simulation results

The mean field theory we have developed can be compared with the simulations by studying the zeroth and first order moments of the probability distributions, i.e.,  $r_0, \overline{N}_1^0, \overline{N}_1^1, \overline{N}_1^2$ . (The probabilities  $r_1$  and  $r_2$  may automatically be obtained from  $r_0$ , since  $r_1 = r_2 = \frac{1-r_0}{2}$ .)

Different values of the mentioned quantities are given in table 1, where the parameters of the models have different values. The reference for this table is the set of

	E. coli	MFT	u=0.05	MFT
$r_0$	$(4.9186 \pm 0.0007) \cdot 10^{-3}$	$4.92705 \cdot 10^{-3}$	$(4.5263 \pm 0.0008) \cdot 10^{-2}$	$4.54635 \cdot 10^{-2}$
$\overline{N_1^0}$	$(2.489 \pm 0.005) \cdot 10^{-2}$	$2.48768 \cdot 10^{-2}$	$0.23862 \pm 0.00014$	$0.238634$
$\overline{N_1^1}$	$4.942 \pm 0.008$	$3.74372$	$4.113 \pm 0.003$	$2.71128$
$\overline{N_1^2}$	$(5.908 \pm 0.007) \cdot 10^{-2}$	$1.25604$	$0.8734 \pm 0.0005$	$2.2774$
	$u = 50, b = 1000$	MFT	$u = 5 \cdot 10^{-8}, b = 10^{-6}$	MFT
$r_0$	$(4.941 \pm 0.004) \cdot 10^{-3}$	$4.95073 \cdot 10^{-3}$	$(2.48 \pm 0.03) \cdot 10^{-3}$	$2.49872 \cdot 10^{-3}$
$\overline{N_1^0}$	$(2.55 \pm 0.06) \cdot 10^{-2}$	$2.48762 \cdot 10^{-2}$	$(2.477 \pm 0.024) \cdot 10^{-2}$	$2.49375 \cdot 10^{-2}$
$\overline{N_1^1}$	$9.89 \pm 0.11$	$2.50019$	$4.92 \pm 0.05$	$4.98751$
$\overline{N_1^2}$	$0.227 \pm 0.013$	$2.49969$	$(5.012 \pm 0.007) \cdot 10^{-5}$	$4.97754 \cdot 10^{-5}$

**Table 1.** Results from different quantities from simulations and mean field theory approach. The values of  $r_0$  and  $\overline{N_1^0}$  predicted by the mean field theory are always in good agreement with the simulations.  $\overline{N_1^1}$  and  $\overline{N_1^2}$  predictions are quite far from the simulation results, except on the limit  $u, b \rightarrow 0$ , where our approximation is exact.

E. coli values, and only the parameters that are changed are written. For the simulations performed,  $r_0$  is always in good agreement with the mean field theory approximation, and so are  $r_1$  and  $r_2$ . Also,  $\overline{N_1^0}$  is in quite good agreement, too.

$\overline{N_1^1}$  and  $\overline{N_1^2}$  are different in the mean field theory, which is an improvement over simpler approximations where they have the same value. However, the values of  $\overline{N_1^1}$  and  $\overline{N_1^2}$  are rather different from the simulations, and this comes from ignoring higher correlations of the numbers of proteins and the state of the switch. Only when  $u, b \rightarrow 0$  are the values in close agreement with the simulation values as expected in this limit where the mean field theory is exact.

Mean field theory can, in principle, be improved by considering higher order moments and correlations. However, the algebra soon gets quite complicated.

#### 4. Exact perturbative solution

In this section we develop a perturbative approach that allows the steady state probabilities  $P_S(N_1, N_2)$  to be computed as a power series in the unbinding rate  $u$ .

##### 4.1. Formal solution

We begin by considering the formal solution of the master equation system (1–3). To transform the system of equations into a system of partial differential equations, we take the generating function of the different probability distributions:

$$K_S(z_1, z_2) = \sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} z_1^{N_1} z_2^{N_2} P_S(N_1, N_2) \quad (44)$$

where  $S = 0, 1, 2$ . In this way we obtain a system of linear partial differential equations with non-constant coefficients:

$$g(z_1 + z_2 - 2)K_0 + [d - (d + b)z_1] \frac{\partial K_0}{\partial z_1} + [d - (d + b)z_2] \frac{\partial K_0}{\partial z_2} + uz_1K_1 + uz_2K_2 = 0 \quad (45)$$

$$[g(z_1 - 1) - u]K_1 + d(1 - z_1) \frac{\partial K_1}{\partial z_1} + d(1 - z_2) \frac{\partial K_1}{\partial z_2} + b \frac{\partial K_0}{\partial z_1} = 0 \quad (46)$$

$$[g(z_2 - 1) - u]K_2 + d(1 - z_1) \frac{\partial K_2}{\partial z_1} + d(1 - z_2) \frac{\partial K_2}{\partial z_2} + b \frac{\partial K_0}{\partial z_2} = 0 \quad (47)$$

where the right-hand side terms have been set to 0, since the stationary probabilities  $P_S(N_1, N_2)$  are the main quantities to be determined in this paper.

The second and the third equation of the system work in a completely analogous way, because of the symmetry of species 1 and 2, so it will be enough to deal with the first two equations. We also note the symmetries  $K_2(z_1, z_2) = K_1(z_2, z_1)$  and  $K_0(z_1, z_2) = K_0(z_2, z_1)$ .

In appendix A we give a formal solution to the system (45–47). However, in practice it is not clear how to actually compute e.g. probability distributions from this solution. In order to do this we develop instead a perturbative approach.

#### 4.2. Perturbative approach

In this section we develop a perturbative approach to the problem of finding the exact stationary state. To do so we require a suitable small parameter of the model which we choose to be  $u$ , the unbinding parameter. In the  $u \rightarrow 0$ , the exact solution is simple: if, for example, one protein of type 1 is bound, the proteins of this kind will obey the usual Poisson distribution regulated by death and birth terms, while the number of proteins of type 2 will just decay to 0. This limit is the starting point for a perturbative solution, wherein the probability distribution will be expanded in a power series of  $u$ :

$$P_S = \sum_{n=0}^{\infty} u^n P_S^{(n)}. \quad (48)$$

Owing to the symmetry of the system  $P_2(N_1, N_2) = P_1(N_2, N_1)$  we need only consider  $P_0$  and  $P_1$ .

Writing out the expansion explicitly we have

$$\begin{aligned} P_1 &= P_1^{(0)} + uP_1^{(1)} \dots \\ P_0 &= uP_0^{(1)} + u^2P_0^{(2)} \dots \end{aligned} \quad (49)$$

Note that the constant term  $P_0^{(0)} = 0$  since  $P_0 = 0$  in the limit of no unbinding.

This approach also makes sense when the typical E. coli values for the parameters are considered [7]:

$$g = 0.05 \quad d = 0.005 \quad b = 0.1 \quad u = 0.005 \quad (50)$$

$u$  is, along with  $d$ , the smallest of the parameters. An expansion in  $1/b$  could also be developed, but we find the expansion in  $u$  more convenient.

### 4.3. Zeroth order

In the zeroth order of the  $u$  expansion of the stationary master equation (3) (with l.h.s set to zero) we find

$$0 = g[P_1^0(N_1 - 1, N_2) - P_1^0(N_1, N_2)] + d[(N_1 + 1)P_1^0(N_1 + 1, N_2) + (N_2 + 1)P_1^0(N_1, N_2 + 1) - (N_1 + N_2)P_1^0(N_1, N_2)] . \quad (51)$$

We define the generating function

$$K_1^{(0)}(z_1, z_2) = \sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} z_1^{N_1} z_2^{N_2} P_1^{(0)}(N_1, N_2) \quad (52)$$

which obeys

$$0 = g(z_1 - 1)K_1^{(0)} + d(1 - z_1)\frac{\partial K_1^{(0)}}{\partial z_1} + d(1 - z_2)\frac{\partial K_1^{(0)}}{\partial z_2} \quad (53)$$

the solution of which is independent of  $z_2$ :

$$K_1^{(0)} = c_1 \exp \frac{g}{d} z_1 \quad (54)$$

where  $c_1$  is a constant to be determined. Analogously  $K_2^{(0)}(z) = c_2 \exp \frac{g}{d} z_2$ . Applying the normalization condition  $K_1^{(0)}(1) + K_2^{(0)}(1) = 1$  and the symmetry consideration  $c_1 = c_2$  leads to

$$K_1^{(0)} = \frac{1}{2} \exp -\frac{g}{d} \exp \frac{g}{d} z_1 . \quad (55)$$

Expanding as a power series in  $z_1, z_2$  yields

$$P_1^{(0)}(N_1, N_2) = \frac{1}{2} \frac{\exp -\frac{g}{d}}{N_1!} \left(\frac{g}{d}\right)^{N_1} \delta_{N_2,0} . \quad (56)$$

This is a Poisson distribution for  $N_1$  with mean  $g/d$ , with  $N_2$  fixed to be zero. The normalisation factor  $1/2$  is so that  $P^{(0)}(N_1, N_2) = P_1^{(0)}(N_1, N_2) + P_2^{(0)}(N_1, N_2)$  is normalised to unity.

### 4.4. General Formulation

We substitute the expansion (48) into the stationary master system (1–3) with time derivatives set equal to zero. Arranging orders of  $u$  the equations may be written as

$$\mathcal{L}_S P_S^{(n)}(N_1, N_2) = -f_S^{(n)}(N_1, N_2) \quad (57)$$

for  $S = 0, 1$  where the action of the linear operators  $\mathcal{L}_S$  is

$$\begin{aligned} \mathcal{L}_0 P_0^{(n)}(N_1, N_2) = & g[P_0^{(n)}(N_1 - 1, N_2) + P_0^{(n)}(N_1, N_2 - 1) - 2P_0^{(n)}(N_1, N_2)] \\ & + d \left[ (N_1 + 1)P_0^{(n)}(N_1 + 1, N_2) + (N_2 + 1)P_0^{(n)}(N_1, N_2 + 1) \right. \\ & \left. - (N_1 + N_2)P_0^{(n)}(N_1, N_2) \right] - b(N_1 + N_2)P_0^{(n)}(N_1, N_2) \end{aligned} \quad (58)$$

$$\begin{aligned} \mathcal{L}_1 P_1^{(n)}(N_1, N_2) = & g[P_1^{(n)}(N_1 - 1, N_2) - P_1^{(n)}(N_1, N_2)] \\ & + d \left[ (N_1 + 1)P_1^{(n)}(N_1 + 1, N_2) + (N_2 + 1)P_1^{(n)}(N_1, N_2 + 1) \right. \\ & \left. - (N_1 + N_2)P_1^{(n)}(N_1, N_2) \right] \end{aligned} \quad (59)$$



and the inhomogenous terms are

$$f_0^{(n)}(N_1, N_2) = P_1^{(n-1)}(N_1 - 1, N_2) + P_2^{(n-1)}(N_1, N_2 - 1) \quad (60)$$

$$f_1^{(n)}(N_1, N_2) = -P_1^{(n-1)} + b(N_1 + 1)P_0^{(n)}(N_1 + 1, N_2) . \quad (61)$$

As noted above, we can first determine the zeroth order  $P_1^{(0)}(N_1, N_2)$  and  $P_2^{(0)}(N_1, N_2) = P_1^{(0)}(N_2, N_1)$  as functions of the parameters of the model. Then, owing to the form of the equation (60),  $f_0^{(1)}$  is determined. This allows us to solve for  $P_0^{(1)}$  which in turn determines  $f_1^{(1)}$  and allows us to solve for  $P_1^{(1)}$ . Continuing in this fashion the rest of the probabilities will be found following the structure:

$$P_1^{(0)} \rightarrow P_0^{(1)} \rightarrow P_1^{(1)} \rightarrow P_0^{(2)} \rightarrow P_1^{(2)} \dots \quad (62)$$

In general,  $P_0^{(n)}$  will be found before  $P_1^{(n)}$ .

Having laid out the general perturbation scheme and established the zeroth order ( $n = 0$ ) solution, we now outline how equations (57) can be solved. We note that for each switch state  $S$  the same linear operator  $\mathcal{L}_S$  appears at all orders  $n$ . This means that the homogeneous parts of the equations are independent of the order (with only the inhomogeneous term on the right hand side varying between orders) and that they only have to be solved once.

#### 4.5. Green function for $\mathcal{L}_0$

Let us define a Green Function  $Q_0(N_1, N_2|N_1^0, N_2^0)$  for the operator  $\mathcal{L}_0$  through

$$\mathcal{L}_0 Q_0(N_1, N_2|N_1^0, N_2^0) = -\delta_{N_1, N_1^0} \delta_{N_2, N_2^0} \quad (63)$$

so that the solution of (57) may be written

$$P_0^{(n)}(N_1, N_2) = \sum_{N_1^0, N_2^0} f_0^{(n)}(N_1^0, N_2^0) Q_0(N_1, N_2|N_1^0, N_2^0) . \quad (64)$$

We define a generating function

$$K_0(z_1, z_2|N_1^0, N_2^0) = \sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} z_1^{N_1} z_2^{N_2} Q_0(N_1, N_2|N_1^0, N_2^0) \quad (65)$$

the equation for which is obtained by summing (63)

$$a(z_1) \frac{\partial K_0}{\partial z_1} + a(z_2) \frac{\partial K_0}{\partial z_2} + g(z_1 + z_2 - 2) K_0 = -z_1^{N_1^0} z_2^{N_2^0} \quad (66)$$

with  $a(z_i) = d - (d + b)z_i$ .

In order to solve (66) we use the method of characteristics (see e.g. [27]). The characteristic equations are

$$\frac{dz_1}{ds} = a(z_1) \quad (67)$$

$$\frac{dz_2}{ds} = a(z_2) \quad (68)$$

$$\frac{dK_0}{ds} = -g(z_1 + z_2 - 2) K_0 - z_1^{N_1^0} z_2^{N_2^0} \quad (69)$$

where  $s$  is a time-like parameter and (67,68) define characteristic curves along which the partial differential equation (66) reduces to the ordinary differential equation (69). Solving (67,68) yields the curves

$$z_1 = \frac{d}{d+b} + Av \quad z_2 = \frac{d}{d+b} + Bv \quad (70)$$

where

$$v = e^{-(d+b)s} \quad (71)$$

and  $A, B$  are two constants to be fixed.

Equation (69) can be rewritten as an ordinary differential equation in  $v$  as

$$\frac{d}{dv} \left[ K_0(v) v^{\frac{2gb}{(d+b)^2}} e^{-\frac{g(A+B)}{(d+b)}v} \right] = \frac{1}{d+b} v^{\frac{2gb}{(d+b)^2}-1} e^{-\frac{g(A+B)}{(d+b)}v} \left( \frac{d}{d+b} + Av \right)^{N_1^0} \left( \frac{d}{d+b} + Bv \right)^{N_2^0}. \quad (72)$$

To integrate (72) we choose an end-point of the integration as  $v = 1$  and set this to correspond to an arbitrary point in the  $z_1$ - $z_2$  plane. This fixes the two constants  $A, B$  as

$$A = z_1 - \frac{d}{d+b} \quad B = z_2 - \frac{d}{d+b}. \quad (73)$$

Thus we obtain

$$K_0(z_1, z_2) = \frac{1}{d+b} \int_0^1 dv v^{\frac{2gb}{(d+b)^2}-1} \exp \left\{ -\frac{g}{d+b} \left( \frac{2d}{d+b} - z_1 - z_2 \right) (1-v) \right\} \\ \times \left( \frac{d}{d+b} (1-v) + v z_1 \right)^{N_1^0} \left( \frac{d}{d+b} (1-v) + v z_2 \right)^{N_2^0}. \quad (74)$$

We now expand as a power series in  $z_1, z_2$  to obtain  $Q_0(N_1, N_2 | N_1^0, N_2^0)$  from (65)

$$Q_0(N_1, N_2 | N_1^0, N_2^0) = \frac{e^{-\frac{2gd}{(d+b)^2}}}{d+b} \sum_{p=0}^{N_1} \frac{1}{p!} \left( \frac{g}{d+b} \right)^p \binom{N_1^0}{N_1-p} \left( \frac{d}{d+b} \right)^{N_1^0-N_1+p} \\ \times \sum_{r=0}^{N_2} \frac{1}{r!} \left( \frac{g}{d+b} \right)^r \binom{N_2^0}{N_2-r} \left( \frac{d}{d+b} \right)^{N_2^0-N_2+r} \\ \times I \left( \frac{2gb}{(d+b)^2} + N_1 - p + N_2 - r, N_1^0 + N_2^0 - N_1 - N_2 + 2p + 2r + 1; \frac{2gd}{(d+b)^2} \right) \quad (75)$$

where  $I(\alpha, \beta; x)$  is defined as the integral

$$I(\alpha, \beta; x) = \int_0^1 dv v^{\alpha-1} (1-v)^{\beta-1} e^{xv} = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)} {}_1F_1(\alpha, \alpha+\beta; x), \quad (76)$$

and  $\Gamma(z)$  and  ${}_1F_1(a, b; z)$  are the usual Euler Gamma function and confluent hypergeometric function respectively.

4.6. Green function for  $\mathcal{L}_1$ 

If we define a Green function for the operator  $\mathcal{L}_1$  through

$$\mathcal{L}_1 Q_1(N_1, N_2 | N_1^0, N_2^0) = -\delta_{N_1, N_1^0} \delta_{N_2, N_2^0} , \quad (77)$$

this equation only has a solution when  $N_2 \neq 0$ . To see this we note that summing the left hand side of (77) over all  $N_1, N_2$  yields zero i.e. the operator conserves probability. Therefore one cannot solve (77) or indeed (57) for an arbitrary right hand side; one requires that the sum of the right hand side of (57) over all  $N_1, N_2$  yields zero. However, since the null space of the operator  $\mathcal{L}_1$  is concentrated on  $N_2 = 0$  (i.e. the stationary state in (56) is proportional to  $\delta_{N_2, 0}$ ) we can find a solution of (77) for  $N_2 > 0$ .

It is simplest to proceed by considering the solution  $P_1$  for an arbitrary right hand side  $-h(N_1, N_2)$

$$\mathcal{L}_1 P_1(N_1, N_2) = -h(N_1, N_2) \quad (78)$$

that satisfies

$$\sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} h(N_1, N_2) = 0 . \quad (79)$$

We define generating functions

$$K_1(z_1, z_2) = \sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} z_1^{N_1} z_2^{N_2} P_1(N_1, N_2) \quad (80)$$

$$H(z_1, z_2) = \sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} z_1^{N_1} z_2^{N_2} h(N_1, N_2) \quad (81)$$

then summing (78) yields

$$d(1 - z_1) \frac{\partial K_0}{\partial z_1} + d(1 - z_2) \frac{\partial K_0}{\partial z_2} + g(z_1 - 1) K_0 = -H(z_1, z_2) . \quad (82)$$

In order to solve (82) we again use the method of characteristics. The characteristic equations are this time

$$\frac{dz_1}{ds} = d(1 - z_1) \quad (83)$$

$$\frac{dz_2}{ds} = d(1 - z_2) \quad (84)$$

$$\frac{dK_1}{ds} = -g(z_1 - 1) K_1 - H(z_1, z_2) . \quad (85)$$

Solving the first two equations yields

$$z_1 = 1 + Av \quad z_2 = 1 + Bv \quad (86)$$

where now

$$v = e^{-ds} \quad (87)$$

and  $A, B$  are constants to be fixed. The final equation becomes

$$\frac{d}{dv} \left[ K_1 e^{-A \frac{g}{d} v} \right] = \frac{H(z_1, z_2)}{dv} e^{-A \frac{g}{d} v} \quad (88)$$

We choose the integration to be from  $v = 0$  to  $v = 1$  where  $v = 0$  corresponds to  $z_1 = z_2 = 1$  and  $v = 1$  corresponds to an arbitrary point in the  $z_1$ - $z_2$  plane which implies  $A = z_1 - 1$  and  $B = z_2 - 1$ . We then obtain the solution of (88)

$$K_1(z_1, z_2) = K_1(1, 1)e^{(z_1-1)\frac{g}{d}} + \frac{1}{d} \int_0^1 dv \frac{e^{(z_1-1)\frac{g}{d}(1-v)}}{v} H(1+(z_1-1)v, 1+(z_2-1)v) . \quad (89)$$

Expanding as a power series in  $z_1, z_2$  implies

$$\begin{aligned} P_1(N_1, N_2) &= K(1, 1)e^{-g/d} \frac{(g/d)^{N_1}}{N_1!} \delta_{N_2, 0} \\ &+ e^{-g/d} \sum_{p=0}^{\infty} \sum_{q=0}^{\infty} \frac{h(p, q)}{d} \binom{q}{N_2} \sum_{r=0}^{N_1} \left(\frac{g}{d}\right)^r \frac{1}{r!} \binom{p}{N_1 - r} \\ &\times I(N_1 + N_2 - r, p + q - N_1 - N_2 + 2r + 1; g/d) . \end{aligned} \quad (90)$$

As discussed above, for  $N_2 > 0$  we can define the Green function (77) by means of which the solution of (78) may be written

$$P_1(N_1, N_2) = \sum_{N_1^0, N_2^0} Q_1(N_1, N_2 | N_1^0, N_2^0) h(N_1^0, N_2^0) . \quad (91)$$

Then we can read off the Green function from (90) as

$$\begin{aligned} Q_1(N_1, N_2 | N_1^0, N_2^0) &= e^{-g/d} \frac{1}{d} \binom{N_2^0}{N_2} \sum_{r=0}^{N_1} \left(\frac{g}{d}\right)^r \frac{1}{r!} \binom{N_1^0}{N_1 - r} \\ &\times I(N_1 + N_2 - r, N_1^0 + N_2^0 - N_1 - N_2 + 2r + 1; g/d) \end{aligned} \quad (92)$$

For  $N_2 = 0$  the solution (90) reads

$$\begin{aligned} P_1(N_1, 0) &= K(1, 1)e^{-g/d} \frac{(g/d)^{N_1}}{N_1!} \\ &+ e^{-g/d} \sum_{p=0}^{\infty} \sum_{q=0}^{\infty} \frac{h(p, q)}{d} \sum_{r=0}^{N_1} \left(\frac{g}{d}\right)^r \frac{1}{r!} \binom{p}{N_1 - r} \\ &\times I(N_1 - r, p + q - N_1 + 2r + 1; g/d) . \end{aligned} \quad (93)$$

Some care is required with the  $r = N_1$  term of the sum in (93) since the integral  $I(0, \beta; x)$  does not converge. However the property (79) of the function  $h$  implies that the coefficient of the offending integral is zero. To see this one can write the  $r = N_1$  term of (93) as

$$\begin{aligned} &e^{-g/d} \sum_{p=0}^{\infty} \sum_{q=0}^{\infty} \frac{h(p, q)}{d} \left(\frac{g}{d}\right)^{N_1} \frac{1}{N_1!} I(0, p+q+N_1+1; g/d) \\ &= \sum_{p=0}^{\infty} \sum_{q=0}^{\infty} \frac{h(p, q)}{d} \left(\frac{g}{d}\right)^{N_1} \frac{1}{N_1!} \int_0^1 dv e^{-\frac{g}{d}(1-v)} v^{-1} (1-v)^{p+q+N_1} \\ &= \sum_{p=0}^{\infty} \sum_{q=0}^{\infty} \frac{h(p, q)}{d} \left(\frac{g}{d}\right)^{N_1} \frac{1}{N_1!} \sum_{s=1}^{p+q} (-1)^s e^{-\frac{g}{d}} \binom{p+q}{s} I(s, N_1 + 1; g/d) . \end{aligned} \quad (94)$$

In the final equality, the binomial expansion of  $(1 - v)^{p+q}$  has been used with the term  $s = 0$  not present since its coefficient vanishes due to (79). All the integrals in (94) then converge.

#### 4.7. First-order results

The first-order contribution to the stationary probability  $P_0^{(1)}(N_1, N_2)$  is given by:

$$P_0^{(1)}(N_1, N_2) = \sum_{N_1^0, N_2^0} f_0^{(1)}(N_1^0, N_2^0) Q_0(N_1, N_2 | N_1^0, N_2^0) \quad (95)$$

with

$$f_0^{(1)}(N_1^0, N_2^0) = \frac{1}{2} \exp\left(-\frac{g}{d}\right) \left[ \left(\frac{g}{d}\right)^{N_1^0-1} \frac{\delta_{N_2^0,0}}{(N_1^0-1)!} + \left(\frac{g}{d}\right)^{N_2^0-1} \frac{\delta_{N_1^0,0}}{(N_2^0-1)!} \right]. \quad (96)$$

Although  $Q_0(N_1, N_2 | N_1^0, N_2^0)$  is expressed in terms of known integrals in (75), it is advisable to go back to the explicit expression of the integrals (76) to evaluate the sums appearing in (95) more easily. In that way,  $P_0^{(1)}(N_1, N_2)$  can be written as:

$$P_0^{(1)}(N_1, N_2) = \frac{1}{2} \frac{e^{-\frac{g}{d} - \frac{2gd}{(d+b)^2}}}{d+b} \sum_{N_1^0=0}^{\infty} \left(\frac{g}{d}\right)^{N_1^0-1} \frac{1}{(N_1^0-1)!} \sum_{p=0}^{N_1} \frac{1}{p!} \left(\frac{g}{d+b}\right)^p \binom{N_1^0}{N_1-p} \left(\frac{d}{d+b}\right)^{N_1^0-N_1+p} \\ \times \frac{1}{N_2!} \left(\frac{g}{d+b}\right)^{N_2} \int_0^1 dv v^{\frac{2gb}{(d+b)^2} + N_1 - p - 1} (1-v)^{N_1^0-N_1+N_2+2p} e^{\frac{2gd}{(d+b)^2}v} + \text{symm} \quad (97)$$

where the label *symm* refers to the fact that there will be another term equal to the written one, apart from a switch in the variables  $N_1^0$  and  $N_2^0$ .

In Appendix B it is shown how the expression may be simplified to the result

$$P_0^{(1)}(N_1, N_2) = \frac{1}{2} \exp\left(\frac{g(b-d)}{(d+b)^2} - \frac{g}{d}\right) \left(\frac{g}{d}\right)^{-1} \frac{1}{d+b} \frac{1}{N_2!} \left(\frac{g}{d+b}\right)^{N_2} \sum_{m=0}^{N_1} \left(\frac{g}{d+b}\right)^{N_1-m} \left(\frac{g}{d}\right)^m \\ \times \frac{1}{(N_1-m)!m!} \left[ \frac{g}{d+b} I\left(\frac{2gb}{(d+b)^2} + m, N_2 + N_1 - m + 2; \frac{g(d-b)}{(d+b)^2}\right) \right. \\ \left. + m I\left(\frac{2gb}{(d+b)^2} + m, N_2 + N_1 - m + 1; \frac{g(d-b)}{(d+b)^2}\right) \right] + \text{symm}. \quad (98)$$

Once we have  $P_0^{(1)}$ , we can plug this result into the  $P_1^{(1)}$  equation which becomes for  $N_2 > 0$

$$P_1^{(1)}(N_1, N_2) = \sum_{N_1^0, N_2^0} f_1^{(1)}(N_1^0, N_2^0) Q_1(N_1, N_2 | N_1^0, N_2^0) \quad (99)$$

where  $f_1^{(1)}(N_1, N_2) = -P_1^{(0)}(N_1, N_2) + b(N_1 + 1)P_0^{(1)}(N_1 + 1, N_2)$ .

We consider separately the two terms of  $f_1^{(1)}$ . The first is

$$-P_1^{(0)}(N_1^0, N_2^0) = -\frac{1}{2} \frac{\exp -\frac{g}{d}}{N_1^0!} \left(\frac{g}{d}\right)^{N_1^0} \delta_{N_2^0,0} \quad (100)$$

Since the calculation with the Green function (see section 4.6) is only for  $N_2 \neq 0$  this term does not contribute and the only contribution comes from the second

term in  $f_1^{(1)}$  involving  $P_0^{(1)}$ . The resulting expression, obtained by substituting  $h = b(N_1 + 1)P_0^{(1)}(N_1 + 1, N_2)$  in (90) with  $P_0^{(1)}$  given by (98), is

$$\begin{aligned}
 P_1^{(1)}(N_1, N_2) = & \frac{b}{2g} \exp\left(\frac{g(b-d)}{(d+b)^2} - \frac{2g}{d}\right) \sum_{N_1^0=0}^{\infty} \sum_{N_2^0=0}^{\infty} (N_1^0 + 1) \left\{ \right. \\
 & \frac{1}{(d+b)} \frac{1}{N_2^0!} \left(\frac{g}{d+b}\right)^{N_2^0} \sum_{m=0}^{N_1^0+1} \left(\frac{g}{d+b}\right)^{N_1^0+1-m} \left(\frac{g}{d}\right)^m \frac{1}{(N_1^0+1-m)!m!} \times \\
 & \left[ \frac{g}{d+b} I\left(\frac{2gb}{(d+b)^2} + m, N_2^0 + N_1^0 - m + 3; \frac{g(d-b)}{(d+b)^2}\right) \right. \\
 & \left. \left. + m I\left(\frac{2gb}{(d+b)^2} + m, N_2^0 + N_1^0 - m + 2; \frac{g(d-b)}{(d+b)^2}\right) \right] + \text{symm}(N_1^0 + 1, N_2^0) \right\} \times \\
 & \left( \binom{N_2^0}{N_2} \sum_{r=0}^{N_1} \left(\frac{g}{d}\right)^r \frac{1}{r!} \binom{N_1^0}{N_1 - r} I(N_1 + N_2 - r, N_1^0 + N_2^0 - N_1 - N_2 + 2r + 1; g/d) \right)
 \end{aligned} \tag{101}$$

Where the symmetric term in this case corresponds to the term inside the curly brackets, exchanging the places of  $N_1^0 + 1$  and  $N_2^0$  coming from the symmetric term in  $P_0^{(1)}$ . For  $N_2 = 0$  we obtain the result shown in (93) and cannot be simplified further.

Equations (93), (98) and (101) are the main results of this section and give closed form expressions for the first-order contributions to the stationary probabilities. The normalization constant  $K(1, 1)$  appearing in (93) is obtained from the condition:

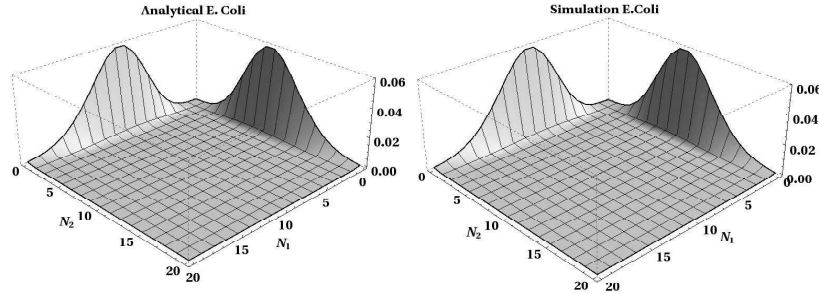
$$\sum_{N_1=0}^{\infty} \sum_{N_2=0}^{\infty} \left[ P_0^{(1)}(N_1, N_2) + P_1^{(1)}(N_1, N_2) + P_2^{(1)}(N_1, N_2) \right] = 0. \tag{102}$$

Once the values of the probabilities  $P_i^{(1)}(N_1, N_2)$  have been obtained numerically, they are multiplied by the unbinding parameter  $u$  and added to the zeroth order probabilities. In that way, the probability distributions  $P_i(N_1, N_2)$  can be computed and plotted up to the first order of the expansion. Figure 4 shows the probability distributions for different values. The agreement is visually good in the first two examples: typical E. coli values (4) and another interesting case, with smaller  $g$ . The order of magnitude is well reproduced in almost every point of the probability distribution. However, the approximation does not work accurately if the value of the unbinding parameter  $u$  is of the order or bigger than the other parameters.

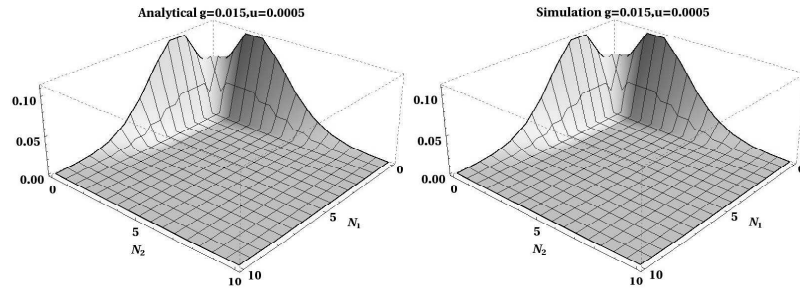
Although the first two examples of figure 4 seem visually in good agreement with the simulations, the best way to check this is to plot different slices of the probability distribution, that is the probability distribution of  $N_2$  where  $N_1$  is held constant (figure 5). We choose the values of  $N_1$  to correspond to the slices with large probability mass, i.e.  $N_1 = 0, 1, 2$  for E. coli values. Figure 5) shows that along the slice with greatest probability mass ( $N_1 = 0$ ) the analytical and simulation plots show good agreement. For  $N_1 > 0$ , there is reasonable agreement for the E. coli values (figure 5 b)), whereas for larger  $u$  the agreement is not so good (figure 5 d)).

Since the proposed method is general, calculations can be performed up to any necessary order to get better results. For example, in the case of E. coli in axes  $N_1 = 1$ ,

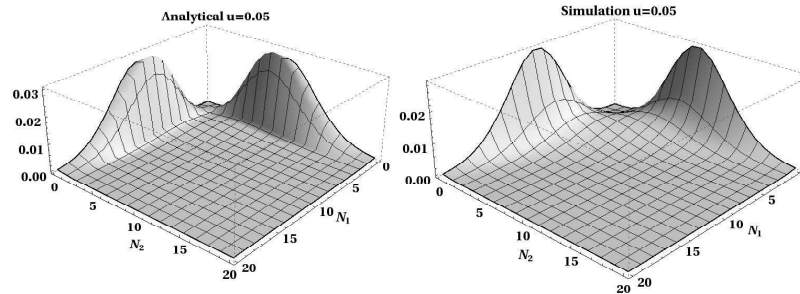
$N_2 = 1$  is enough to compute the second order to have very good results (figure 6). In general, the method can be iterated as many times as required.



a) E. coli values.



b)  $g = 0.015, u = 0.0005, d = 0.005, b = 0.1$ .



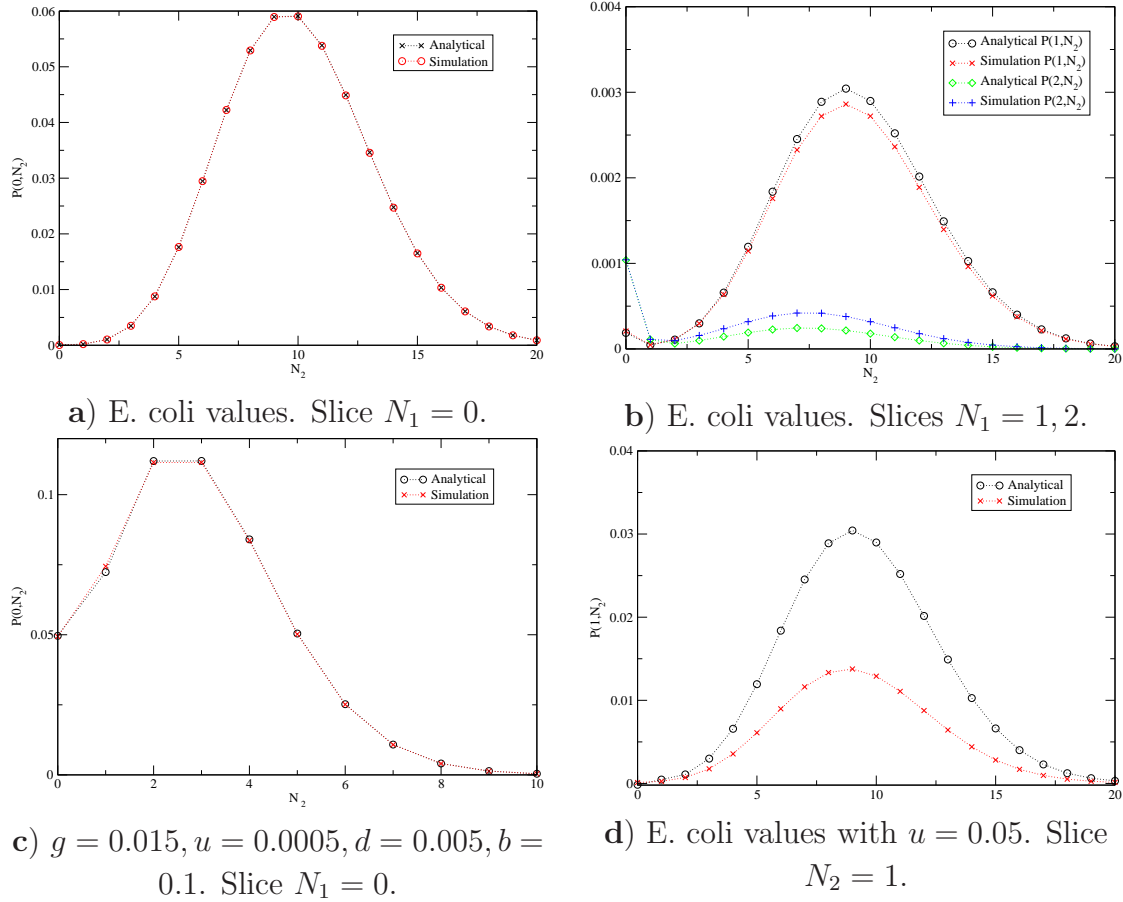
c) E. coli values with  $u = 0.05$ .

**Figure 4.** Comparison between the analytical first order and the simulation distributions for different values of the parameters a) E. coli values (4). The probability distributions have the same shape and the order of magnitude is well reproduced in almost every point. b)  $g = 0.015, u = 0.0005, d = 0.005, b = 0.1$  The order of magnitude is again well reproduced. In this case, the two peaks get closer to the origin as the ratio  $g/d$  is smaller. c) E. coli values with  $u = 0.05$ . The approximation at first order is no longer accurate as the value of  $u$  is no longer small compared to the rest of the parameters of the model.

## 5. Conclusion

The exclusive genetic switch presented in this paper represents a minimal model of two populations that compete in an indirect way, that is, through a common promoter site that when occupied by a member of one population stops the production of the other.



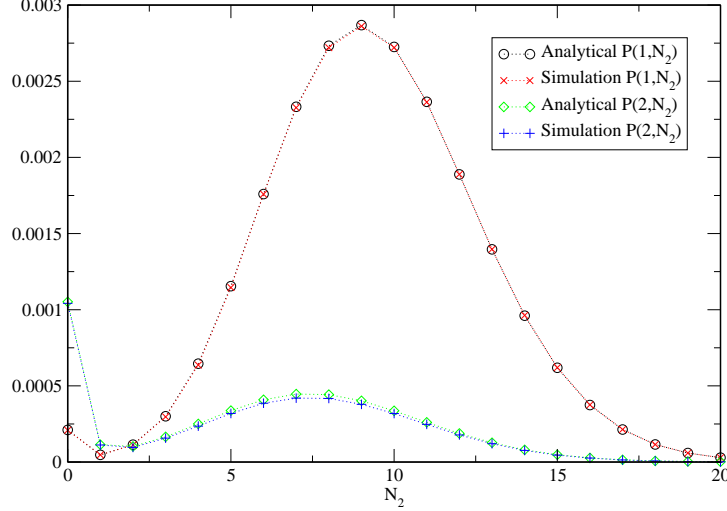


**Figure 5.** Comparison between the analytical probability distributions  $P(N_1^*, N_2)$  where  $N_1^*$  is fixed and chosen to correspond to slices with largest probability mass. The agreement in slice  $N_1 = 0$  is good for both figures a) and c). There is some quantitative difference in b), which corresponds to the E. coli values in slices with less probability mass. This is improved with second order calculations, as can be seen in figure 6. In d) the difference is clear, since the first order approximation is no longer accurate, as discussed in figure 4. The error in the values is negligible and, in all the cases, is smaller than the size of the used symbols.

It is a non-equilibrium system because the microscopic processes are irreversible and detailed balance does not hold. The non equilibrium stationary state exhibits interesting properties of bistability i.e. generically at any given time the system is dominated by one of the populations. We have developed two main analytical approaches to study the stationary state: a mean field theory and an exact perturbative approach. In addition we have presented some exactly solvable limits. We also have studied the system and checked the analytical results by using Monte Carlo simulations.

These simulations show that the symmetry of the system is always broken, that is, the system is always functioning as a switch, with two opposite states in which one population is much more abundant than the other. This holds generically except in the limit  $u, b \rightarrow \infty$  where the state is symmetric. As the relevant parameters for the switch become smaller, the probability of finding bound proteins decreases,

**Figure 6.** Comparison between the probability slices  $P(1, N_2)$  and  $P(2, N_2)$  from second order analytical calculations and simulations, for E. coli values. The second order is clearly enough to get accurate results.



but the distributions always remain asymmetric, showing no phase transition between asymmetric and symmetric states

The mean field theory of section 3 is based on exact moment equations which are factorised at the level of second moments. The approximation scheme is constructed to be exact in the limiting parameter case of vanishing binding/unbinding rates  $b$ ,  $u$  with the binding constant  $k = \frac{b}{u}$  held constant. The theory shows good agreement with some quantities obtained from the simulation, but there are some other quantities whose agreement varies and depends on the value of the parameters. The mean-field theory could be improved upon by systematically considering higher order moments and correlations.

As a first attempt, to our knowledge, at an exact solution of this nonequilibrium system we have developed an exact perturbative approach which consists of an expansion in the unbinding rate  $u$ . We computed the expansion to first order and this has allowed us to obtain the whole probability distribution for the typical E. coli and other values, in good agreement with the simulations. Higher orders can be obtained systematically by iterating the proposed method. The analytical expressions at first order (98,101) already illustrate the complexity of the nonequilibrium stationary state. In principle, the Green functions that have been calculated in Section 4 allow the expansion to be carried out to arbitrary order although analytical expressions for the higher order terms in the expansions might be long or difficult to simplify. However, they still can be computed numerically by programming the proposed operations and, in principle, the method can be iterated as many times as necessary to get more accurate results.

In this paper we have not attempted to study the dynamics, but it would be of interest to do so. In particular the dependence of the flip time or first passage time (the time for the system to change from being dominated by one population to the other) on

the parameter values is of interest. It may be possible to extend our analytical solution to consider such flip times and to provide estimate of first passage times between the two bistable states. It might be that the Green functions we have computed in section 4 contain some useful dynamical information.

The techniques that we have developed should be applicable to the understanding of other related systems and properties of genetic switches in general. The factorisation of the moment equation hierarchy is straightforward to implement to obtain a mean field theory; the exact perturbative approach is more involved but can be used in general for problems with similar probability distributions, as long as the Green functions are analytically solvable. Thus the techniques represent standard procedures to analyze this class of systems.

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## Appendix A. Analytical method for systems of linear PDEs.

According to [27], there is a way to solve, or at least simplify, a system of linear first-order partial differential equations. First of all, considering a three dimensional space with a vector  $\vec{K}(z_1, z_2)$  for the three probabilities, the system has to be written as:

$$A(z_1, z_2) \frac{\partial \vec{K}(z_1, z_2)}{\partial z_1} + B(z_1, z_2) \frac{\partial \vec{K}(z_1, z_2)}{\partial z_2} = C(z_1, z_2) \vec{K}(z_1, z_2) + \vec{d}(z_1, z_2) \quad (\text{A.1})$$

where  $A, B$  and  $C$  are  $3 \times 3$  matrices, and  $\vec{d}$  and  $\vec{K}$  are column matrices. The requirement to solve the system is that  $\det A(z_1, z_2) \neq 0$  or  $\det B(z_1, z_2) \neq 0$ .

In this case the expression of the matrices is:

$$\begin{aligned} A(z_1, z_2) &= \begin{pmatrix} d - (d+b)z_1 & 0 & 0 \\ b & d(1-z_1) & 0 \\ 0 & 0 & d(1-z_1) \end{pmatrix} \\ B(z_1, z_2) &= \begin{pmatrix} d - (d+b)z_2 & 0 & 0 \\ 0 & d(1-z_2) & 0 \\ b & 0 & d(1-z_2) \end{pmatrix} \\ C(z_1, z_2) &= \begin{pmatrix} -g(z_1 + z_2 - 2) & -uz_1 & -uz_2 \\ 0 & -[g(z_1 - 1) - u] & 0 \\ 0 & 0 & -[g(z_2 - 1) - u] \end{pmatrix} \\ \vec{d}(z_1, z_2) &= \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \end{aligned} \quad (\text{A.2})$$

This is not the most general system that could be written with this notation, since the matrix  $\vec{d}$  is zero, and  $A$  and  $B$  only depend on  $z_1, z_2$ , respectively.

The requirement to solve the system is that  $\det A(z_1, z_2) \neq 0$  or  $\det B(z_1, z_2) \neq 0$ , which is fulfilled almost in every point. Multiplying by the matrix  $B^{-1}$ , the matrix  $A$  is transformed into:

$$A' = B^{-1}A = \begin{pmatrix} \frac{d-(d+b)z_1}{d-(d+b)z_2} & 0 & 0 \\ \frac{b}{d(1-z_2)} & \frac{(1-z_1)}{1-z_2} & 0 \\ \frac{-b[d-(d+b)z_1]}{d(1-z_2)(d-(d+b)z_2)} & 0 & \frac{(1-z_1)}{1-z_2} \end{pmatrix} \quad (\text{A.3})$$

whose eigenvalues, written as columns in a matrix  $R$  are:

$$R = \begin{pmatrix} 0 & 0 & \frac{-d(z_1 - z_2)}{d(z_1 - 1) + bz_1} \\ 0 & 1 & \frac{d - (d+b)z_2}{d - (d+b)z_1} \\ 1 & 0 & 1 \end{pmatrix} \quad (\text{A.4})$$

This hyperbolic system can be transformed with elementary matrix operations:

$$C' = B^{-1}C \quad \vec{K} = R(z_1, z_2)\vec{v} \quad (\text{A.5})$$

The method then states that the components of  $v$  obey the following system of equations:

$$\frac{dv_i}{dz_2} = \sum_{j=0}^2 \hat{c}_{ij}v_j \quad (\text{A.6})$$

where  $\hat{c}_{ij}$  are the components of the matrix  $C'$  once we have performed the transformation with  $R$ :  $\hat{C} = R^{-1}C'R$ .

As can be seen from the last equation, we have uncoupled the derivative terms and, even if this system cannot be solved analytically, it is easier to deal with it computationally. The problem itself can be written as:

$$\begin{aligned} \frac{dv_0}{dz_2} &= \left[ \frac{(g+u)z_1 - gz_2}{d(z_1 - z_2)} \right] v_0 + \left[ \frac{uz_1(z_1 - 1)}{d(z_1 - z_2)(z_2 - 1)} \right] v_1 \\ &\quad + \left[ \frac{-dg(z_1 - 1)^2 + b[d - (g+u)z_1 + gz_1z_2]}{d(z_2 - 1)[d(z_1 - 1) + bz_1]} \right] v_2 \\ \text{on } \frac{dz_1}{dz_2} &= \frac{1 - z_1}{1 - z_2} \\ \frac{dv_1}{dz_2} &= \left[ \frac{uz_2}{d(z_2 - z_1)} \right] v_0 + \left[ \frac{(z_1 - 1)[-gz_1 + (g+u)z_2]}{d(z_2 - z_1)(z_2 - 1)} \right] v_1 \\ &\quad + \left[ \frac{dg(z_2 - 1)^2 + b[-d + (g+u)z_2 - gz_1z_2]}{d(z_2 - 1)[d(z_1 - 1) + bz_1]} \right] v_2 \\ \text{on } \frac{dz_1}{dz_2} &= \frac{1 - z_1}{1 - z_2} \\ \frac{dv_2}{dz_2} &= \left[ \frac{uz_1}{d(z_2 - z_1)} + \frac{u}{d - (d+b)z_2} \right] v_0 + \left[ \frac{uz_1[d(z_1 - 1) + bz_1]}{d(z_1 - z_2)(d - (b+d)z_2)} \right] v_1 \\ &\quad + \left[ \frac{-u + g(z_1 + z_2 - 2)}{d(z_2 - 1)[d(z_2 - 1) + bz_2]} \right] v_2 \\ \text{on } \frac{dz_1}{dz_2} &= \frac{d - (d+b)z_1}{d - (d+b)z_2} \end{aligned} \quad (\text{A.7})$$

Although this method in principle solves exactly the system of partial differential equations it appears a formidable task to actually integrate equations (A.7).

**Appendix B. Derivation of expression (98)**

In this appendix we give the detailed derivation of (98). We begin from (97)

$$P_0^{(1)}(N_1, N_2) = \frac{1}{2} \frac{e^{-\frac{g}{d} - \frac{2gd}{(d+b)^2}}}{d+b} \sum_{N_1^0=0}^{\infty} \left(\frac{g}{d}\right)^{N_1^0-1} \frac{1}{(N_1^0-1)!} \sum_{p=0}^{N_1} \frac{1}{p!} \left(\frac{g}{d+b}\right)^p \binom{N_1^0}{N_1-p} \left(\frac{d}{d+b}\right)^{N_1^0-N_1+p} \\ \times \frac{1}{N_2!} \left(\frac{g}{d+b}\right)^{N_2} \int_0^1 dv v^{\frac{2gb}{(d+b)^2} + N_1 - p - 1} (1-v)^{N_1^0 - N_1 + N_2 + 2p} e^{\frac{2gd}{(d+b)^2}v} + \text{symm} \quad (\text{B.1})$$

where the label *symm* refers to the fact that there will be another term equal to the written one, apart from a switch in the variables  $N_1^0$  and  $N_2^0$ .

Now defining:

$$c(v) \equiv v^{\frac{gb}{(d+b)^2}} e^{-\frac{gd}{(d+b)^2}(1-v)}, \quad m \equiv N_1 - p, \quad r(v) \equiv \frac{d}{d+b} \frac{1-v}{v}, \quad s(v) \equiv \frac{g}{d+b} (1-v) \quad (\text{B.2})$$

we arrive at the expression (for convenience we will drop the dependence of the previous functions on  $v$ ):

$$P_0^{(1)}(N_1, N_2) = \int_0^1 \frac{dv}{v(d+b)} \sum_{N_1^0=0}^{\infty} \frac{1}{2} \exp\left(-\frac{g}{d}\right) \left(\frac{g}{d}\right)^{N_1^0-1} \frac{c^2}{(N_1^0-1)!} \\ \sum_{m=0}^{N_1} \binom{N_1^0}{m} r^{N_1^0-m} v^{N_1^0} \times \frac{1}{(N_1-m)!} s^{N_1-m} \frac{s^{N_2}}{(N_2)!} + \text{symm} \quad (\text{B.3})$$

Separating the parts of the expression that can be summed, the following simplification can be obtained by changing the order of the sums appropriately:

$$\sum_{N_1^0=0}^{\infty} \left(\frac{g}{d}\right)^{N_1^0-1} \frac{1}{(N_1^0-1)!} v^{N_1^0} \sum_{m=0}^{N_1} \binom{N_1^0}{m} \frac{r^{N_1^0-m} s^{N_1-m}}{(N_1-m)!} \\ = \left(\frac{g}{d}\right)^{-1} \sum_{m=0}^{N_1} \frac{s^{N_1-m}}{(N_1-m)!} \sum_{N_1^0=m}^{\infty} \binom{N_1^0}{m} \frac{r^{N_1^0-m}}{(N_1^0-1)!} \omega^{N_1^0} \\ = \left(\frac{g}{d}\right)^{-1} \sum_{m=0}^{N_1} \frac{s^{N_1-m}}{(N_1-m)! m!} \sum_{n=0}^{\infty} \frac{(n+m)}{n!} r^n \omega^{m+n} \quad (\text{B.4}) \\ = \left(\frac{g}{d}\right)^{-1} \sum_{m=0}^{N_1} \frac{s^{N_1-m}}{(N_1-m)! m!} \omega^m \sum_{n=0}^{\infty} \left( \frac{(r\omega)^n}{(n-1)!} + \frac{m(r\omega)^n}{n!} \right) \\ = \left(\frac{g}{d}\right)^{-1} \sum_{m=0}^{N_1} \frac{s^{N_1-m}}{(N_1-m)! m!} \omega^m (s+m) e^s$$

where  $\omega = vg/d$ . Note that this sum could be simplified further, but that the simplification will not allow us to perform the integration over  $v$  in closed form. In this and following equation, we will try to obtain the simplest expressions globally, knowing that simplifying one part can lead to further complications in another.

Plugging this sum into the  $P_0^{(1)}$  equation and writing all the explicit forms of the functions, we obtain the result (98).